Oral Glucose Tolerance Test (OGTT) among type 1 diabetic Siblings and Control group

فحص احتمالية السكر الفموي لدى كل من أشقاء النوع الأول لمرضى السكري ومجموعة السيطرة

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الخلاصة:
خلفية البحث : يلعب العامل الوراثي دوراً أساسيا للإصابة بمرض السكر لذلك نجد أن أشقاء النوع الأول لمرضى السكري قد يكونون أكثر عرضة لاعتلال الفحص الفموي لاحتمالية السكر.
الهدف: لتحديد ما إذا كان الأشقاء المصابين بالسكري قد اجروا اختبار تحمل السكر ومقارنتهم مع المجموعة الضابطة.
المنهجية : في دراسة مقارنة أجريت على 120 شخص قسموا إلى ثلاث مجاميع (مرضى السكري، أقارب الدرجة الأولى و مجموعة السيطرة) كل مجموعة مكونة من 40 شخصاً اختيروا خلال مراجعتهم إلى مركز السكري في مستشفى الزهراء التعليمي في الكوت للفترة من نيسان/2012 إلى نيسان/2013.
النتائج : أجري فحص احتمالية السكر الفموي(OGTT) الى المجاميع الغير مصابة بمرض السكري و أظهرت النتائج بأن معدل ال OGTT يتمتع بفارق معنوي كبير(significant P value 0.000) لدى كلتا المجموعتين في حين لا يوجد فارق معنوي (non-significant P value 0.288) بمعدل الأختلاف للOGTT بالرغم من أن معدل الاختلاف كان أعلى لدى أقارب الدرجة الأولى(25.3250) بالمقارنة بمجموعة السيطرة (22.0750).
الاستنتاج : أن العامل الوراثي قد يكون مسؤولاً عن الإصابة بالنوع الأول لمرض السكري كون أن الأشقاء أظهروا أعتلالاً بالفحص الفموي لاحتمالية السكر.
التوصيات : لغرض الكشف المبكر عن الإصابة بالنوع الأول لمرض السكري يجب أن يجرى فحص احتمالية السكر الفموي (OGTT) لكل أشقاء المصابين بذلك المرض.

Abstract:
Background: the genetic factor of type 1 diabetes mellitus may play a key role in pathogenesis of that disorder, thus, diabetic siblings might prone into an impaired OGTT.
Objective: To determine whether diabetic Siblings might have an impaired glucose tolerance test in compare to normal control group.
Material and Method: A case-control study was performed on 120 persons, they divided into three group which are diabetic, siblings and control (40 persons in each group), who attended to Al Zahraa Teaching Hospital /Diabetic Center in Al Kut between the period from April; 2012 till April; 2013.
Results: OGTT performed on both diabetic siblings and control, results have showed that the Means of OGTT is highly Significant (P value = 0.000) in both Siblings and Control groups, whereas there were no Significant differences in the Means of differences of OGTT in both tested groups (Siblings and Control), P value = 0.288, although the Mean of differences of OGTT is higher in Siblings group (25.3250) than that in Control group (22.0750).
Conclusion: the inheritance factor play a key role in pathogenesis of type 1 diabetes mellitus since, diabetic siblings showed an impaired OGTT.
Recommendation: for early detection of diabetes, diabetic siblings must submit to a routine screening test by OGGT.
Key words: Type 1 diabetes mellitus, Siblings, OGTT.

INTRODUCTION

Type 1 diabetes is an autoimmune disorder in which the destruction of insulin-producing beta-cells can be detected years before the clinical manifestation of the disease [1]. Selective autoantibody assays and metabolic testing can now identify first degree relatives of type I diabetic patients, in whom the risk of diabetes is over 80% at 5 years [2,3]. The ability to identify subjects at risk makes the exploration of immune intervention strategies to halt or even prevent Beta-cell destruction a major goal. The clinical manifestation of type 1 diabetes usually involves symptoms such as polyuria and polydipsia and is thought to occur after autoimmune destruction of most of the pancreatic B-cells, resulting in severe insulin deficiency and fasting hyperglycemia. However, investigators in the Diabetes Prevention Trial of Type 1 Diabetes (DPT-1) [4,5] have detected a group of subjects with type 1 diabetes who have a different phenotype. These subjects are asymptomatic, have normal (<6.1 mmol/l) or impaired (6.1–<7.0 mmol/l) fasting glucose on their oral glucose tolerance tests (OGTTs), but have 2-h glucose values >11.1 mmol/l, thus meeting one of the American Diabetes Association's [6] new criteria for the diagnosis of diabetes. Importantly, these subjects have characteristics placing them at increased risk for type 1 diabetes; i.e., they are relatives of patients with type 1 diabetes, they are <45 years of age, and they are islet cell antibody (ICA)-positive. The DPT-1 is a multicenter randomized trial designed to determine if type 1 Diabetes can be prevented or delayed. First- or second-degree relatives of type 1 diabetic patients ≤ 45 years of age are screened for the presence of ICAs. Then, those who are ICA+ enter the staging part of the DPT-1, during which they undergo tests to estimate their risk for developing diabetes more precisely. The last staging test performed before randomization into the treatment part of their study there is an OGTT to rule out the presence of diabetes [4, 5]. Those with fasting or postprandial hyperglycemia on this OGTT are excluded from further participation. This report describes the population of subjects with type 1 diabetes identified by the 2-h OGTT criteria alone at the time of the DPT-1 staging OGTT. Demographic data (age, sex, and relationship to proband), immune activity (antibody status), and tests of B-cell function (first-phase insulin response [FPIR] and OGTT) are described for these subjects and compared with those subjects whose staging OGTT for DPT-1 classified them as having normal glucose tolerance (NGT) or impaired glucose tolerance (IGT).Carla J. *et al.*, (2001), [7] describe a previously unrecognized group of subjects with asymptomatic type 1 diabetes. These subjects have normal or impaired fasting glucose values and elevated 2-h glucose values on OGTT. The validity of their observation is indicated by the fact that there is no absolute difference or trend of higher values in fasting glucose among those with NGT, IGT, and diabetes diagnosed by 2-h glucose alone, despite moderate (IGT) or marked (diabetic) 2-h hyperglycemia. In addition, repeat OGTT was performed on 14 subjects with diabetes diagnosed by 2-h OGTT criteria alone, and either IGT or diabetes with normal fasting glucose was confirmed in 13 of the subjects. Importantly, these subjects have characteristics associated with type 1 diabetes; they are relatives of subjects with type 1 diabetes, they are between 3 and 45 years of age, they are ICA+, and 53% have markedly abnormal first-phase insulin release. Although the use of FPG is simpler and more reproducible [8, 9], the omission of the 2-h PG will miss a proportion of diabetic subjects who have normal FPG but elevated 2-h PG (> or equal to 11.1 mmol/l) [10]. They have suggested using the paired values of FPG and HbA1c to identify potential diabetic subjects [11](Ko GTC. Only those with high FPG (6.1–6.9 mmol/l) and high HbA1c (> or equal to 6.1%) required an OGTT to confirm diabetes. With use of this approach, > 80% of OGTTs could be saved [12]. Hence, they followed up on 208 nondiabetic subjects and examined their rates of progression to diabetes. They analyzed their likelihood of becoming diabetic according to their baseline FPG and HbA1c concentrations.

OBJECTIVE:

To determine whether diabetic Siblings might have an impaired glucose tolerance test in compare to normal control group.

PATIENTS AND METHOD

This study was performed on 120 persons, selected randomly with matched age and sex, with male to female ratio ½, who were attended to Al Zahraa Teaching Hospital /Diabetic Center in Al Kut between the periods from April, 2012 till April, 2013.

- Three study groups were investigated which included:
- **First group:** Forty patients with IDDM, fulfilling inclusion criteria for IDDM (1. younger age less than 35 yrs., 2. Positive family history. 3. Positive HLA association. 4. Autoimmune association and Positive antibody to B-cells (ICA). 5. Low BMI less than 18.5, 6.FBS >120 mg/dl , RBS >180-200 mg/dl and HbA1c > 6 plus clinical signs and symptoms) [12]
- **Second group:** Forty relatives (Sibling) of IDDM patients had no history or clinical evidence of IDDM or any autoimmune disease.
- **Third group:** Forty healthy control group who had no history or clinical evidence of IDDM or any autoimmune disease.

Oral glucose tolerance test were performed for both Diabetic Siblings and Control groups using a Glucose powder manufactured by the State Company for the Drugs Industry and Medical Appliances Samarra-Iraq.

Preparation before the test:

1. Unrestricted carbohydrate diet for 3 days.
2. Fasted overnight for at least 8 hrs.
3. Rest for 30 mins.
4. Remain seated for the duration of the test, with no smoking.

Sampling:

Plasma glucose is measured before and 2 hrs after a 75 g oral glucose drink [13].

RESULTS:

Table (1): OGTT before and after 75 g of oral glucose drink in Siblings group:

Group	OGTT	Mean	No.	Std. Deviation	Std. Error Mean	P. value
Siblings	OGTT before	87.9250	40	14.17724	2.24162	0.000
	OGTT 2hrs after	1.1325E2	40	23.50095	3.71583	

Table (1) show the Data that collected and tested by Independent sample T-test and Paired T-test. Results showed that the means of OGTT is highly significant (P value = 0.000) in between siblings and control groups, whereas there were no significant differences in the means of differences of OGTT in both tested groups (siblings and control), P value = 0.288, although the mean of differences of OGTT is higher in siblings group (25.3250) than that in control group (22.0750).

Table (2): OGTT before and after 75 g of oral glucose drink in Control group:

Group	OGTT	Mean	No.	Std. Deviation	Std. Error Mean	P.value
Control	OGTT before	91.7000	40	15.28733	2.41714	0.000
	OGTT 2hrs after	1.1378E2	40	21.28378	3.36526	

Table (2) show the Data that collected and tested by Independent sample T-test and Paired T-test. Results showed that the means of OGTT is highly significant (P value = 0.000) in between siblings and control groups, whereas there were no significant differences in the means of differences of OGTT in both tested groups (siblings and control), P value = 0.288, although the mean of differences of OGTT is higher in siblings group (25.3250) than that in control group (22.0750).

Table (3): Means of differences in OGTT between Sibling and Control group:

Group	No.	Mean of difference OGTT	Std. Deviation	Std. Error Mean	P.value
sibling	40	25.3250	15.37295	2.43068	0.288
control	40	22.0750	11.54120	1.82482	0.288

Table (3) show the Data that collected and tested by Independent sample T-test and Paired T-test. Results showed that the means of OGTT is highly significant (P value = 0.000) in between siblings and control groups, whereas there were no significant differences in the means of differences of OGTT in both tested groups (siblings and control), P value = 0.288, although the mean of differences of OGTT is higher in siblings group (25.3250) than that in control group (22.0750), Table (3.3, 3.4, and 3.5).

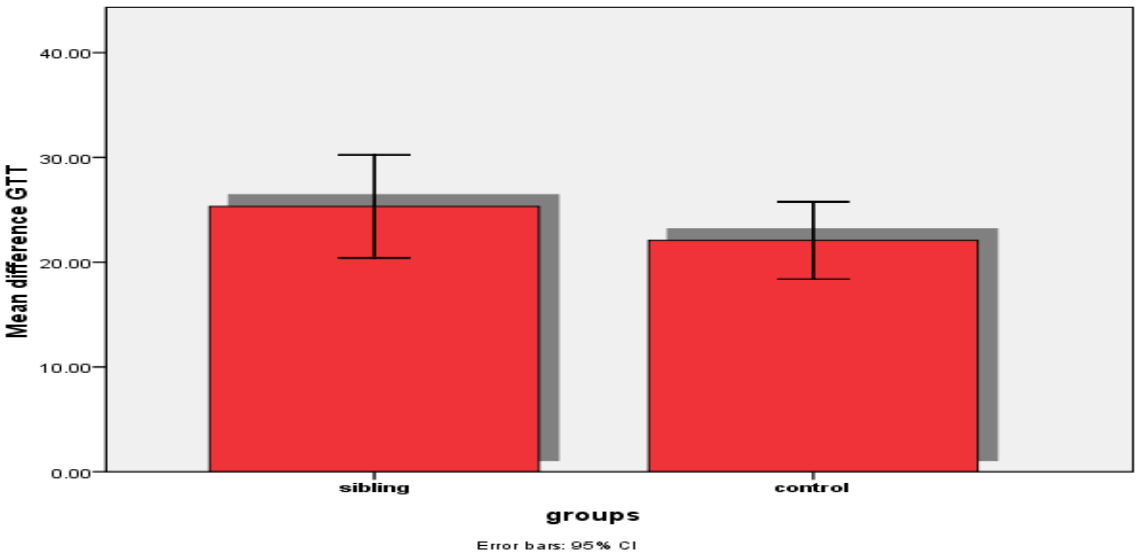

Figure (1): Means of differences in OGTT between Sibling and Control group:

Figure (1) shows the mean of differences in OGTT among both diabetic siblings and control that is higher in sibling group than that in control group.

DISCUSSION:

The results in this study showed that the means of OGTT is highly significant (P value = 0.000) in between siblings and control groups, whereas there were no significant differences

in the means of differences of OGTT in both tested groups (siblings and control), P value = 0.288, although the mean of differences of OGTT is higher in siblings group (25.3250) than that in control group (22.0750), Table (1, 2 and 3).These results agreed with Bingley PJ. *et al.*, (1994), Verge CF. *et al.*, (1996), whom stated that selective autoantibody assays and metabolic testing could now identify first degree relatives of type I diabetic patients, in whom the risk of diabetes is over 80% at 5 years [2,3]. The ability to identify subjects at risk makes the exploration of immune intervention strategies to halt or even prevent beta-cell destruction a major goal. The investigators in the diabetes prevention trial of type 1 diabetes (DPT-1) have detected a group of subjects with type 1 diabetes who have a different phenotype [4, 5]. These subjects are asymptomatic, have normal (<6.1 mmol/l) or impaired (6.1–<7.0 mmol/l) fasting glucose on their oral glucose tolerance tests (OGTTs), but have 2-h glucose values >11.1 mmol/l, thus meeting one of the American diabetes association's new criteria for the diagnosis of diabetes, importantly, these subjects have characteristics placing them at increased risk for type 1 diabetes; i.e., they are relatives of patients with type 1 diabetes, they are <45 years of age, and they are islet cell antibody (ICA)-positive [6]. This is totally agreed with the results that obtained in our study.

The agreement is going with those results obtained by Carla J. *et al.*, (2001), who describe a previously unrecognized group of subjects, with asymptomatic type 1 diabetes. These subjects had normal or impaired fasting glucose values and elevated 2-h glucose values on OGTT. The validity of their observation is indicated by the fact that there is no absolute difference or trend of higher values in fasting glucose among those with NGT, IGT, and diabetes diagnosed by 2-h glucose alone, despite moderate (IGT) or marked (diabetic) 2-h hyperglycemia. In addition, repeated OGTT was performed on 14 subjects with diabetes diagnosed by 2-h OGTT criteria alone, and either IGT or diabetes with normal fasting glucose was confirmed in 13 of the subjects. Importantly, these subjects have characteristics associated with type 1 diabetes; they were relatives of subjects with type 1 diabetes, between 3 and 45 years of age, ICA+, and 53% of them had markedly abnormal first-phase insulin release [7]. The results that obtained in the present study is not going with New Zealand Screaning System of Diabetes (NZSSD) which now recommends the use of HbA1c to diagnose diabetes in most circumstances. Compared with the oral glucose tolerance test (OGTT) or fasting glucose alone, HbA1c offers substantial advantages of the lack of need for fasting, reduced biological variability and an equally good relationship with increased retinopathy and CVD risk [14, 15]. The glucose-based criteria are also limited by high variability of blood glucose, particularly for the 2-hour value post OGTT. There are also issues relating to sample collection, processing and analytical requirements that are often poorly addressed. There is also concern regarding the validity of the standard 75g OGTT for all ages, sizes and genders. OGTTs are more expensive than HbA1c, as well as being laborious and time consuming for both patients and laboratories. HbA1c however can be misleading in some circumstances – e.g. falsely low in patients with increased red blood cell turnover or post blood transfusion and falsely high in some haemoglobinopathies as well as some ethnic differences in rate of Hbglycation [16]. The current glucose-based diagnostic criteria remain unchanged, but the NZSSD recommends that the OGTT should only be used when there is uncertainty about the validity of HbA1c measures in specific patients - for example in the presence of haemoglobinopathy or abnormal red cell turnover - or where there are special clinical reasons.Because the performance of an oral glucose tolerance test (OGTT) is time consuming, laborious, and poorly reproducible [17, 18, 11].The american diabetes association (ADA) recently recommended a moving away from the OGTT to using fasting plasma glucose (FPG) as a diagnostic criterion [6], which seems to be disagreed with results that obtained in our study which showed a potential advantage of the use of OGTT in detection of high risk group from the first degree relatives in suspicion of diabetic thus, the omission of

the 2-h PG will miss a proportion of diabetic subjects who have normal FPG but elevated 2-h PG (> or equal to 11.1 mmol/l) [10]. Also the results of this study were disagreed with Ko GTC. *et al.*, (1998), who had suggested the using of the paired values of FPG and HbA1c to identify potential diabetic subjects.

Only those with high FPG (6.1–6.9 mmol/l) and high HbA1c (> or equal to 6.1%) required an OGTT to confirm diabetes. With the use of this approach, > 80% of OGTTs could be saved [11]. They followed up 208 nondiabetic subjects and examined their rates of progression to diabetes. They analyzed their likelihood of becoming diabetic according to their baseline FPG and HbA1c concentrations, which seemed to be not related to OGTT results in our study.

CONCLUSION

Diabetic Siblings are more liable for development of diabetes in future since the mean of OGTT higher in them rather than control group.

RECOMMENDATION

OGTT should be included as screening test to elicit the highly risky group from diabetic Siblings.

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